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Joan Claybrook, President

October 19, 2000

Janet Woodcock, MD
Director, Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Woodcock:

We hereby petition the FDA for an immediate ban of all uses of phenylpropanolamine (PPA) in over-the-counter products (OTC) including as the active ingredient in appetite suppressants and as a decongestant in cough/cold preparations. This petition is submitted pursuant to a) 21 CFR, Section 10.30 and b) sections 355 (e) and 314.150 of the Federal Food, Drug and Cosmetic Act.¹ As an over-the-counter drug ingredient, the only way PPA would be able to stay on the market would be if FDA continues to believe that it is safe and effective. Abundant evidence from well over 100 published reports about the dangers of PPA, added to the current industry-funded Yale study that found "PPA increases the risk for hemorrhagic stroke",² and reports in FDA's adverse reaction system of at least 51 cases of hemorrhagic stroke in PPA users make it clear the drug cannot be considered safe. In fact, FDA's Office of Post-Marketing Drug Risk Assessment (OPDRA) has concluded that "PPA should not be generally recognized as safe"³ and that Office has made a recommendation that "PPA containing appetite suppressants [and] ...cough/cold remedies should no longer be available as over-the-counter products."⁴

In conversations with me and in public presentations you have stated that an important ongoing function for the FDA is to remove older, outmoded drugs when they no longer serve any unique purpose and when there is evidence of their danger. PPA is such a drug that has been available for at least 53 years if not longer.⁵ I completely agree in the continuing relevance of the 1979 advice from the Medical Letter, an independent periodical that evaluates drug therapy--"There is no good evidence that phenylpropanolamine...or any other drug can help obese patients achieve long-term weight reduction. The only satisfactory treatment for obesity is a life-long change in patterns of food intake and physical activity."⁶ The decongestant use of PPA, while effective, makes no sense because there are many safer, equally effective alternatives such as pseudoephedrine or, safer yet, nose sprays or drops used for no more than three days.⁷ PPA is clearly an older drug, which should be immediately removed from the market. I hope this will be accomplished as quickly as possible. The longer the delay, the larger the toll of preventable strokes and other serious damage to the public.

¹ FDA regulations for over-the-counter (OTC) drugs specify that all ingredients are either class I, generally recognized as safe and effective, class II, not generally recognized as safe and effective, or class III, inadequate evidence to make a determination.

² Phenylpropanolamine and Risk of Hemorrhagic Stroke: Final Report from the Hemorrhagic Stroke Project, May 10, 2000. Page 3.

³ Undated memo from OPDRA epidemiologists Drs. Lois La Grenade and Parivash Nourjah to Dr. Charles Ganley, Director of FDA's Division of OTC Drug Products (probably August, 2000).

⁴ Memo from OPDRA epidemiologists Drs. Lois La Grenade and Parivash Nourjah to Dr. Charles Ganley, Director of FDA's Division of OTC Drug Products, September 27, 2000.

⁵ In a 1947 edition of the Physicians' Desk Reference (PDR), a Merck product, Propadrine, which contains PPA, is listed as a nasal decongestant.

⁶ The Medical Letter 1979;21:65-66.

⁷ Ingredients include oxymetazoline, xylometazoline, phenylephrine.

Ralph Nader, Founder

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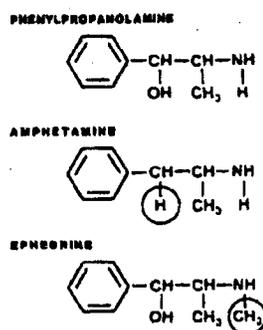


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The background for the recent, well-designed Yale epidemiological study that found "PPA increases the risk for hemorrhagic stroke",⁸ includes a long history of published serious adverse events including hemorrhagic strokes attributed to PPA going back to 1979. These cases can be attributed to the drug because they usually occur shortly after ingestion of PPA and because of the lack of other plausible explanations, especially in otherwise healthy younger people.

Additionally, there has been evidence for the specific mechanism by which these PPA-induced cerebral hemorrhages occur. Similar evidence has existed for more than 20 years for the stroke-producing properties of amphetamines, once the most common drugs used for obesity. Both PPA and amphetamines are known to cause cerebral vasculitis, a severe inflammation of the blood vessels in the brain, which, in combination with the blood-pressure-raising effects of the drugs, can result in cerebral or subarachnoid brain hemorrhages and strokes.⁹ In addition to strokes, other serious adverse reactions attributed to PPA include acute psychosis, convulsions, acute renal failure, heart damage and hypertension.

The following chart shows the close chemical structures of PPA, ephedrine and amphetamine:



The well-documented concerns about the cardiac (arrhythmias) and brain toxicity of ephedrine (also associated with a large number of strokes due to bleeding in the brain), the known brain toxicity of amphetamine and the use of amphetamine as an appetite suppressant confirm that there are pharmacological as well as chemical similarities among these compounds.

Ten years ago, a review of published cases of adverse reactions attributed to PPA found 142 such cases in 85 different publications, including 24 intracranial (cerebral or subarachnoid) hemorrhages, eight seizures, and eight deaths, most due to stroke. The most common adverse effects were symptoms compatible with acute hypertension, with severe headache the most frequent complaint. About two-thirds of all adverse reactions occurred in females and two-thirds in patients under 30.¹⁰

Further information about PPA and strokes comes from FDA's spontaneous adverse reaction reporting system. In an FDA memo dated August 6, 1991, FDA medical officer Dr. Heidi Jolson reported that there had been a total of 44 cases of stroke (35 hemorrhagic) in PPA-users reported to the FDA until then. This included 15 reports of strokes in people using PPA-containing diet pills from the files of diet pill manufacturer Thompson Medical Company¹¹ which had not previously (before early 1991) been sent to the FDA, because such submission was not required. An update of the adverse reactions reported to the FDA attached to a September 27, 2000 memo from epidemiologists in OPDRA stated that an additional 16 cases of hemorrhagic stroke associated with PPA, just in people from age 18 to 47, had been reported to the FDA from 1991 until July, 2000.¹² With estimates that the percent of cases of OTC adverse drug reactions which

⁸ Phenylpropanolamine and Risk of Hemorrhagic Stroke: Final Report from the Hemorrhagic Stroke Project, May 10, 2000. Page 3.

⁹ Rumbaugh CL, et al. Cerebral vascular changes secondary to amphetamine abuse in the experimental animal. (And discussion of human cases). *Radiology* 1971;101:345-351. Forman HP, et al. Cerebral vasculitis and hemorrhage in an adolescent taking diet pills containing phenylpropanolamine: case report and review of literature. *Pediatrics* 1989;83:737-741. Kase CS, et al. Intracerebral hemorrhage and phenylpropanolamine use. *Neurology* 1987;37:399-404. Lake CR, et al. Transient hypertension after two phenylpropanolamine diet aids and the effects of caffeine: a placebo-controlled follow-up study. *Am J Med* 1989; 86: 427-432.

¹⁰ Lake CR, et al. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* 1990; 89:195-208.

¹¹ Jolson memo 8/6/91 in FDA vol 1 handout.

¹² Memo from OPDRA epidemiologists Drs. Lois La Grenade and Parivash Nourjah to Dr. Charles Ganley, Director of FDA's Division of OTC Drug Products, September 27, 2000.

are sent to the FDA are between 5% and 10% of those that actually occur, this total of at least 51 reported cases of hemorrhagic stroke (35+16) may mean as many as 510 to 1020 cases have actually occurred in people using PPA-containing products.

As far as the CHPA-funded Yale study, the results are quite clear and, in the context of all that was previously known about the role of PPA in causing strokes, they come as no surprise. The methodological criticisms of the study are somewhat overshadowed by the fact that the same consultants who now are raising those criticisms could have presumably been retained by CHPA before it signed off on the design and details of the study. For every case-control study, there are always those who will find something wrong with it, because it lacks the "perfection" of a randomized controlled trial. What is notable, however, is that when case-control studies are found to implicate a drug or a device in connection with a disease, there is an extraordinarily skewed representation of industry-funded critics there to say nay, or maybe not.

PPA is just another example in a long history of many serious public health hazards caused by drugs or medical devices which were allowed to continue endangering people much longer than they should--after sufficient evidence for action was available--because of industry-funded nit-picking with the methodology of the studies, often case-control studies, such as the one being discussed today.

Other examples in which we pleaded the case for FDA action long before it was eventually taken include: aspirin and Reye's syndrome, hyperabsorbent tampons and toxic shock, DES and clear-cell vaginal cancer in DES daughters, and menopausal estrogens and uterine cancer. Eventually, action to ban or restrict was taken in each of these instances but much later than it should have been.

Even without any case-control or other epidemiological study, in an even larger number of cases, the number and specificity of cases reports of serious drug-induced diseases including death was well documented. However, here too, bans or restrictions on use were delayed because of drug-industry (and its experts') attempts to deny or trivialize the causal role of the drugs and because of FDA delays in proper regulatory action. Examples of this include Rezulin, Duract, Propulsid, Posicor, Grepafloxacin, and Trovafloxacin, and the Bjork-Shiley heart valve.

It has been more than 20 years since the first alarms were raised about the dangers of PPA and about the fact that there is no evidence in the long term that diet drugs such as PPA actually help to lose and retain weight losses. A 1981 study found that people who were on a weight reduction drug (fenfluramine) alone or the drug combined with behavior therapy or behavior therapy alone lost comparable amounts of weight. But they found that behavior therapy alone patients regained significantly less than pharmacotherapy patients or those who had the combined treatment, suggesting that the use of the drug actually retarded the beneficial effects of behavior therapy.¹³ Around the same time, the Medical Letter, an independent periodical which evaluates drug therapy, wrote: "There is no good evidence that phenylpropanolamine...or any other drug can help obese patients achieve long-term weight reduction. The only satisfactory treatment for obesity is a life-long change in patterns of food intake and physical activity."¹⁴

Many early researchers who investigated PPA commented that the drug should not be available over-the-counter. One group of researchers stated, in 1987, that "The over-the-counter availability of PPA-containing medications may be inappropriate and in need of revision, since it does not appear to be in keeping with current standards of public safety."¹⁵ Since then, hundreds or more American patients have suffered strokes, psychotic episodes, heart damage and other known adverse effects of PPA for no documented benefit in the long term.

In light of the voluminous medical literature documenting the life-threatening adverse effects of PPA such as hemorrhagic strokes and the confirmatory evidence of this in the industry-funded

¹³ Craighead LW, et al. Behavior therapy and pharmacotherapy for obesity. Arch Gen Psychiatry 1981 Jul;38(7):763-768.

¹⁴ The Medical Letter 1979;21:65-66.

¹⁵ Kase CS, et al. Intracerebral hemorrhage and phenylpropanolamine use. Neurology 1987;37:399-404.

epidemiological study, it is not possible for PPA to remain in the OTC category of safe and effective (category I). Thus, since all of this evidence mandates and FDA's OPDRA has concluded, "PPA should not be generally recognized as safe,"¹⁶ the only choice is to remove the drug from all OTC products. We hope this will be accomplished as quickly as possible. The longer the delay, the larger the toll of preventable strokes and other serious damage to the public.

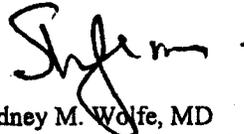
ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,



Sidney M. Wolfe, MD
Director, Public Citizen's Health Research Group

¹⁶ Undated memo from OPDRA epidemiologists Drs. Lois La Grenade and Parivash Nourjah to Dr. Charles Ganley, Director of FDA's Division of OTC Drug Products (probably August, 2000).